PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07D 405/12, A61K 31/4525 — A1

(11) International Publication Number: **WO 00/27844**

(43) International Publication Date: 18 May 2000 (18.05.00)

(21) International Application Number: PCT/GB99/03664

(22) International Filing Date: 5 November 1999 (05.11.99)

(30) Priority Data:
9824298.5 5 November 1998 (05.11.98) GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: CAMBURN, Ian, David [GB/GB]; SmithKline Beecham Pharmaceuticals, Clarendon Road, Worthing, West Sussex BN14 8QH (GB). MERRIFIELD, David, Roy [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). VALDER, Christopher, Edmund [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: WEST, Vivien; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: PROCESS FOR THE PREPARATION OF PAROXETINE HYDROCHLORIDE

(57) Abstract

Solid forms of paroxetine hydrochloride (crystalline as well as amorphous) are obtained by precipitation from a supercritical or near–critical fluid such as carbon dioxide. This procedure offers the advantage of a more easily controlled precipitation process than is obtained by previously known methods, and better control of surface morphology, porosity, particle size and distribution.

This procedure offers the advantage of a more easily controlled precipitation process than is obtained by previously known methods, and better control of surface morphology, porosity, particle size and distribution. These factors are important and affect, for example, the rate of dissolution and the performance of the material in secondary pharmaceutical manufacturing.

Paroxetine hydrochloride is prepared for supercritical fluid precipitation by forming a solution in a supercritical fluid such as supercritical carbon dioxide. Other supercritical fluids such as ethane, n-propane, n-butane, and nitrogen oxide, may also be used. Known solid forms of paroxetine hydrochloride form such solutions with some difficulty. Therefore the paroxetine hydrochloride is preferably first dissolved in an auxiliary solvent, for example ethanol, propan-2-ol, or isobutyl alcohol, compatible with the supercritical fluid, and the solution brought into contact with the supercritical fluid to form a suitable solution for precipitation. A suitable solution may be prepared from amorphous paroxetine hydrochloride or a crystalline anhydrate, hydrate, or solvate of paroxetine hydrochloride, or by dissolving the free base and hydrochloric acid in an aqueous, organic or mixed aqueous and organic solvent. Indeed it may be possible to bring the free base and hydrochloric acid together in the supercritical domain where they may react prior to precipitation of paroxetine hydrochloride.

In order to achieve successful precipitation of paroxetine hydrochloride from a supercritical fluid by a method that uses an auxiliary solvent, this solvent preferably has an affinity for the supercritical fluid so that both may be effectively removed in a single process. The preferred auxiliary solvents listed above are not ideal in this respect, at least when the supercritical fluid is carbon dioxide, so it may be advantageous to employ an additional entraining solvent to confer suitable properties on the auxiliary solvent. An example of a suitable entraining solvent for use with propan-2-ol and supercritical carbon dioxide is acetone.

The entraining solvent may be combined with the auxiliary solvent in a ratio from 1:5 to 20:1, preferably from 1:1 to 10:1, and most preferably from 3:1 to 7:1. The concentration of paroxetine hydrochloride in the auxiliary solvent may be from 0.5% to 25%, but is preferably in the range 1% to 10%, for example from 2.5% to 5%. The supercritical solution for precipitation is formed by combining the paroxetine hydrochloride solution with supercritical fluid in its liquid phase in a ratio of from 1:2 to 1:200, preferably in the range from 1:10 to 1:50, most preferably in the range 1:15 to 1:30.

In a typical procedure, a chamber containing a spray device is maintained at a temperature and pressure such that carbon dioxide (or other fluid) is supercritical. The temperature is controlled using an oven, and the pressure is controlled using a back pressure regulator at the chamber exit. A solution of paroxetine hydrochloride is prepared in a suitable solvent system and this solution and a supercritical fluid are separately metered to the spray device using high pressure pumps. Within, or close to the spray device, the supercritical fluid effectively removes the solvent from the paroxetine hydrochloride solution, giving a precipitate which is deposited in the collection chamber. When sufficient material has accumulated in the collection chamber the delivery of paroxetine hydrochloride solution is stopped. The paroxetine hydrochloride particles are rinsed with supercritical fluid to remove final traces of solvent and the apparatus is depressurised to harvest the product.

In an alternative method of operation the paroxetine hydrochloride is dissolved in the supercritical fluid or solvent-modified supercritical fluid using a saturator chamber. The resultant supercritical fluid solution is sprayed through a spray device into a second chamber at atmospheric or slightly above atmospheric pressure and particles of paroxetine hydrochloride are formed.

The temperature of the precipitation is generally from 15°C to 150°C, preferably from 45°C to 100°C, and the pressure is maintained in the range 25 to 300 bar, preferably from 100 to 200 bar.

When a crystalline product is desired, improved control of the precipitation process may be achieved by the addition of seeds. When the desired product is a hydrate such as paroxetine hydrochloride hemihydrate, an amount of water should be present in excess of the amount required according to theory.

The solid product of this invention may be formulated for therapy in the dosage forms described in EP-A-0223403 or WO96/24595. Free-flowing solids are advantageous for the preparation of solid formulations. Easily soluble solids are suitable for the preparation of solutions for parenteral use.

Therapeutic uses of the paroxetine product of this invention include treatment of: alcoholism, anxiety, depression, obsessive compulsive disorder, panic disorder, chronic pain, obesity, senile dementia, migraine, bulimia, anorexia, social phobia, pre-menstrual syndrome (PMS), adolescent depression, trichotillomania, dysthymia, and substance abuse, referred to below as "the disorders".

Accordingly, the present invention also provides:

a pharmaceutical composition for treatment or prophylaxis of the disorders comprising solid paroxetine hydrochloride obtained by the process of this invention and a pharmaceutically acceptable carrier or a solution of the obtained solid paroxetine hydrochloride;

the use of solid paroxetine hydrochloride obtained by the process of this invention to manufacture a medicament in solid or liquid form for the treatment or prophylaxis of the disorders; and

a method of treating the disorders which comprises administering an effective or prophylactic amount of solid paroxetine hydrochloride obtained by the process of this invention, or a solution thereof, to a person suffering from one or more of the disorders.

The invention is illustrated by the following Examples:

Example 1

A particle collection chamber incorporating a spray device was maintained at a temperature of 45°C and a pressure of 95 bar. A 2% solution of paroxetine hydrochloride in a 50:10 acetone/propan-2-ol mixture containing 1.6% water was metered to the spray device at 0.40 ml/min. Supercritical carbon dioxide was also metered to the spray device at 9.0 ml/min. Paroxetine hydrochloride was deposited as low bulk density white powder.

Example 2

A particle collection chamber with a spray device was maintained at 50°C and 125 bar. A 2% solution of paroxetine hydrochloride in 110:10 acetone/propan-2-ol was metered to the spray device at 0.27 ml/min. Supercritical carbon dioxide was also metered to the spray device at 6.0 ml/min. Paroxetine hydrochloride was deposited as a dense white powder.

CLAIMS:

1. A process for isolating a solid form of paroxetine hydrochloride which comprises precipitating paroxetine hydrochloride from a solution thereof in a supercritical or near-critical fluid

2. A process according to claim 1 in which the solid form of paroxetine hydrochloride is crystalline.

3. A process according to claim 1 or 2 in which the supercritical fluid is carbon dioxide or ethane, n-propane, n-butane, or nitrogen oxide.

4. A process according to claim 1, 2 or 3 in which the paroxetine hydrochloride is first dissolved in an auxiliary solvent compatible with the supercritical fluid, and the solution brought into contact with the supercritical fluid to form a suitable solution for precipitation.

5. A process according to claim 4 in which the auxiliary solvent is ethanol, propan-2-ol, or isobutyl alcohol.

6. A process according to claim 4 or 5 in which an additional entraining solvent is employed to confer suitable properties on the auxiliary solvent.

7. A process according to claim 6 in which the supercritical fluid is carbon dioxide, the auxiliary solvent is propan-2-ol, and the entraining solvent is acetone.

8. A pharmaceutical composition for treatment or prophylaxis of the disorders comprising solid paroxetine hydrochloride obtained by the process of this invention and a pharmaceutically acceptable carrier or a solution of the obtained solid paroxetine hydrochloride.

9. The use of solid paroxetine hydrochloride obtained by the process of this invention to manufacture a medicament in solid or liquid form for the treatment or prophylaxis of the disorders.

10. A method of treating the disorders which comprises administering an effective or prophylactic amount of solid paroxetine hydrochloride obtained by the process of this invention, or a solution thereof, to a person suffering from one or more of the disorders.

INTERNATIONAL SEARCH REPORT

Inter ...nal Application No
PCT/GB 99/03664

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D405/12 A61K31/4525

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 24595 A (SMITHKLINE BEECHAM PLC ;JACEWICZ VICTOR WITOLD (GB); WARD NEAL (GB) 15 August 1996 (1996-08-15) cited in the application page 6, line 5 - line 10; claims ---	1-10
A	WO 98 31365 A (WARD NEAL ;JACEWICZ VICTOR WITOLD (GB); SMITHKLINE BEECHAM PLC (GB) 23 July 1998 (1998-07-23) ---	1-10
A	EP 0 223 403 A (BEECHAM GROUP PLC) 27 May 1987 (1987-05-27) cited in the application examples --- -/--	1,8-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 January 2000	24/01/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	De Jong, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/GB 99/03664

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 810 224 A (ASAHI GLASS CO LTD) 3 December 1997 (1997-12-03) cited in the application claim 1	1,8-10
A	WO 95 01221 A (UNIV BRADFORD ;HANNA MAZEN (GB); YORK PETER (GB)) 12 January 1995 (1995-01-12) abstract	1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/03664

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims: it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter ›nal Application No
PCT/GB 99/03664

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9624595 A	15-08-1996	AU 701518 B	28-01-1999
		AU 4332896 A	15-08-1996
		AU 4786496 A	27-08-1996
		AU 9821398 A	04-03-1999
		BE 1009112 A	05-11-1996
		BG 100333 A	30-08-1996
		BR 9600534 A	13-05-1997
		CA 2168829 A,C	07-08-1996
		CA 2210022 A	07-08-1996
		CA 2210023 A,C	07-08-1996
		CA 2211521 A	07-08-1996
		CA 2211522 A	07-08-1996
		CH 688353 A	15-08-1997
		CH 689229 A	31-12-1998
		CN 1143643 A	26-02-1997
		CY 2015 A	20-02-1998
		CZ 9600320 A	14-08-1996
		DE 19603797 A	14-08-1996
		DE 29623383 U	20-05-1998
		DK 11996 A	07-08-1996
		EP 0808314 A	26-11-1997
		ES 2114471 A	16-05-1998
		FI 960519 A	07-08-1996
		FR 2730232 A	09-08-1996
		GB 2297550 A,B	07-08-1996
		GR 1002466 B	06-11-1996
		HK 59397 A	16-05-1997
		HU 9600255 A	28-03-1997
		IE 960104 A	07-08-1996
		IT MI960203 A	05-08-1997
		JP 2915338 B	05-07-1999
		JP 8245620 A	24-09-1996
		JP 11228571 A	24-08-1999
		LT 96007 A,B	25-10-1996
		LU 88711 A	23-08-1996
		LV 11618 A	20-12-1996
		LV 11618 B	20-04-1997
		MC 2411 A	02-12-1996
		NL 1002248 C	11-09-1996
		NL 1002248 A	06-08-1996
		NO 960472 A	07-08-1996
		NZ 280943 A	29-01-1997
		PL 312646 A	19-08-1996
		PT 101827 A,B	30-09-1996
		RO 112426 A	30-09-1997
		SE 9600406 A	07-08-1996
		SG 43787 A	14-11-1997
		SI 9600036 A	31-10-1996
WO 9831365 A	23-07-1998	AU 5567398 A	07-08-1998
		EP 0952831 A	03-11-1999
		NO 993460 A	14-09-1999
EP 0223403 A	27-05-1987	AU 593295 B	08-02-1990
		AU 6433286 A	30-04-1987
		BG 61323 B	30-05-1997
		CA 1287060 A	30-07-1991
		CZ 9103910 A	19-01-1994

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter onal Application No
PCT/GB 99/03664

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0223403 A		CY 1743 A	17-02-1995
		DE 3688827 A	09-09-1993
		DE 3688827 T	31-03-1994
		DK 61091 A	05-04-1991
		DK 508786 A	26-04-1987
		ES 2058061 T	01-11-1994
		FI 864320 A,B,	26-04-1987
		HK 125993 A	19-11-1993
		IE 59901 B	20-04-1994
		JP 1918281 C	07-04-1995
		JP 6047587 B	22-06-1994
		JP 62129280 A	11-06-1987
		NO 864237 A,B,	27-04-1987
		NZ 218047 A	29-03-1989
		PT 83608 A,B	01-11-1986
		US 4721723 A	26-01-1988
EP 0810224 A	03-12-1997	CA 2206592 A	30-11-1997
		JP 10045756 A	17-02-1998
WO 9501221 A	12-01-1995	AT 174530 T	15-01-1999
		AU 677345 B	17-04-1997
		AU 7007194 A	24-01-1995
		CA 2166301 A	12-01-1995
		DE 69415320 D	28-01-1999
		DE 69415320 T	24-06-1999
		EP 0706421 A	17-04-1996
		ES 2128564 T	16-05-1999
		GR 3029612 T	30-06-1999
		JP 8511987 T	17-12-1996
		NZ 267697 A	26-05-1997
		SG 47392 A	17-04-1998
		US 5851453 A	22-12-1998